REMARKS

Reconsideration and withdrawal of the rejections of the application are requested in view of the herein amendments, arguments and submissions.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 18-25 are pending in this application. Support for the amendments to claims 18 and 20-24 can be found throughout the specification, and are made mostly to address formal issues. Support for the recitation "coronary or peripheral vessels" is found throughout the specification, and specifically, for example, in the title of the invention and on page 1, lines 13, 17 and 20. No new matter is added.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims are in full compliance with the requirements of 35 U.S.C. §112. Amendments to the claims are not made for the purpose of patentability within the meaning of 35 U.S.C. §§§§101, 102, 103 or 112. Rather, these changes are made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the herewith amendments should not give rise to any estoppel, as the herewith amendments are not narrowing amendments.

II. THE REJECTIONS UNDER 35 U.S.C. §112, 2ND PARAGRAPH, ARE OVERCOME

Claims 1, 3-5, 8-11 and 18-33 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. The Office Action alleges that "the term 'restenosis' may be used to indicate many different types of pathological conditions besides coronary restenosis". Claims 18 and 22 have been amended to specify that the restenosis is of coronary or peripheral blood vessels, as is discussed throughout the specification, and indeed, is included in the title of the application. It is submitted that this amendment obviates the rejection, and reconsideration and withdrawal are requested.

III. THE REJECTION UNDER 35 U.S.C. §103 IS OVERCOME

Claims 1, 3-5 and 8-11 and 18-33 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Inoue *et al.* and Maisonpierre *et al.* in view of Kendall *et al.* and Asahara *et al.* and in further view of Hanahan. The rejection is traversed.

Initially, it should be appreciated that restenosis and atherosclerosis are distinct conditions. Atherosclerosis is the build-up of various plaques (cholesterol, fat, calcium, cellular

debris) which decreases the internal diameter of an artery, reducing the blood supply to the heart, brain and other vital organs. It proceeds from an initial endothelial damage that results in the recruitment and migration of monocytes to the site of the injury. Growth factors are released which induce medial smooth muscle cells to proliferate and migrate to the inside of the vessel. The factors associated with atherosclerosis include: high levels of cholesterol, triglycerides and low density lipoproteins (LDL), and low levels of high density lipoproteins (HDL).

Like atherosclerosis, restenosis also results in a dangerous narrowing of vessels, but proceeds via a different mechanism from atherosclerosis. Restenosis is a complication in the maintenance of vessel patency after angioplasty in coronary and other vessels. It is a consequence of multiple factors, including vessel recoil, negative vascular remodeling, residual plaque burden, and hyperplasia in the inner surface of the vessel. Hyperplasia is due to the migration and proliferation of smooth muscle cells with subsequent deposition of extracellular matrix components at the site of injury, resulting in a thickening of the vessel wall. The claims have been limited to the reduction of restenosis, so the subsequent discussion will focus on that aspect of the invention.

Applicants are fully aware that it is the combination of references that is being set forth as allegedly rendering the pending claims obvious; however, without a discussion of the points made in each individual reference, there is no way to address the assertions in the Office Action. The Examiner seems to be drawing his own relevant "points to learn" from the references, without necessarily considering their teachings as a whole.

Nevertheless, Inoue relates entirely to atherosclerosis, specifically, the localization of VEGF in atherosclerotic plaques and its potential role in recruiting macrophages to said plaques. While Inoue suggests that neovascularization may also play a role in atherosclerosis, there is no such suggestion with respect to restenosis. In fact, restenosis is not mentioned by Inoue at all.

Since the *point to learn* from Kendall is that a soluble VEGF receptor can serve as a VEGF inhibitor (Office Action at page 4), this reference obviously does not make up for the deficiency of Inoue. Indeed, restenosis and possible methods for its reduction are not taught or suggested at all in Kendall.

The same is true for Maisonpierre, which, as is stated on page 5 of the Office Action, relates to the opposing roles of Ang1 and Ang2, and suggests that therapeutic manipulation of vessel growth is likely to require simultaneous regulation of both the VEGF and angiopoietin

systems. Likewise, Asahara explores combinations of angiopoietin and VEGF, and their role in neovascularization. Again, reduction of restenosis is not addressed in either reference; rather, the references relate solely to angiogenesis. Hanahan, newly cited in this Office Action, does not supply the missing claim elements.

The Office Action asserts, on page 5, that "the Inoue reference teaches that VEGF is capable of inducing neointimal angiogenesis and intimal hyperplasia, and may promote process of atherosclerosis, and that the coronary occlusive lesions have extensive neovascularization." The Office Action makes then makes a leap of reasoning and states that "angiogenesis is a part of the pathology of restenosis or atherosclerosis, a regiment of anti-angiogenesis is indicated and would be beneficial", even though the Inoue reference makes no connection at all between angiogenesis and restenosis. In fact, as is attested to in the attached Declaration under 37 CFR 1:132 by Dr. Stephen Epstein, an inventor of this application and an expert in the field, there has been no demonstration in the prior art of a causal relationship between neovascularization and restenosis, and no studies have ever shown that prevention of angiogenesis leads to prevention of restenosis.

Therefore, since atherosclerosis and restenosis are distinct conditions, having independent mechanisms of development, they cannot be likened to one another as equivalent pathologies. The treatment of one cannot necessarily be extrapolated to treat the other, and no evidence to the contrary has been provided. That being the case, the combination of references cited in the Office Action does not render the claims obvious, as it does not disclose every element of the pending claims. In particular, any teaching or suggestion of reducing restenosis using the combination of a VEGF inhibitor and a vessel maturation inducer is lacking, as restenosis is not so much as mentioned in any of the cited references. In view of these facts, reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a) are requested.

CONCLUSION

In view of the remarks and amendments herewith, the application is believed to be in condition for allowance, or at least in better condition for appeal. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date.

Respectfully submitted,

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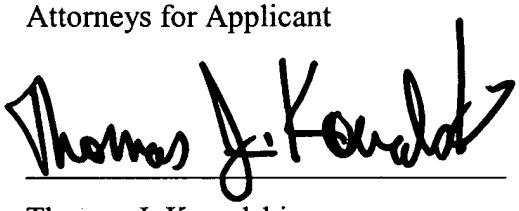

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